PB85-101772

Toxicological Evaluation of Selected Chlorinated Phenols

Medical Coll. of Virginia, Richmond

Prepared for

Health Effects Research Lab., Cincinnati, OH

Sep 84

U.S. Department of Commerce
National Technical Information Service
NTIS

PB85-101772

EPA-600/D-84-234
September 1984

TOXICOLOGICAL EVALUATION OF SELECTED CHLORINATED PHENOLS

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Supported by U.S.E.P.A. Grant R-808861010

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OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
RESEARCH TRIANGLE PARK, NC 27711

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NATIONAL TECHNICAL
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U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO. EPA-600/D-84-234	2.
3. RECIPIENT'S ACCESSION NO. PB85 101772	
4. TITLE AND SUBTITLE Toxicological Evaluation of Selected Chlorinated Phenols	5. REPORT DATE September 1984
	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S) Borzelleca, Condie*, and Hayes	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS Dept. Pharmacology and Toxicology, Medical College of Virginia, Richmond, VA 23298 *TOTB/TMD/HERL/ORD/USEPA, 26 West St. Clair Street, Cincinnati, OH 45268	10. PROGRAM ELEMENT NO. ABMC1A
	11. CONTRACT/GRANT NO. CR808861
12. SPONSORING AGENCY NAME AND ADDRESS HERL/ORD/USEPA Research Triangle Park, NC 27711	13. TYPE OF REPORT AND PERIOD COVERED Proceedings
	14. SPONSORING AGENCY CODE EPA-600/11

15. SUPPLEMENTARY NOTES

16. ABSTRACT

Toxicology studies were conducted with the mono-, di-, and pentachlorophenols (CP). Chlorophenols (except PC) demonstrate a relatively low order of toxicity. The order of toxicity in mice and rats (most to least) is: PCP > tetra CPs > mono CPs > tri CPs > di CPs. Short-term (14 days) repeated exposure to 2-CP at (gavage) doses of 35, 69, or 175 mg/kg/day (approximately 1/10, 1/5, 1/2 the acute oral LD_{50}) resulted in 100% lethality at the highest dose and no biologically significant compound related effects at the lower doses. Short-term (14 days) repeated exposure to 2,4-DCP at (gavage) doses of 64, 128, or 638 mg/kg/day (approximately 1/20, 1/10, 1/2 the acute oral LD_{50}) failed to induce significant compound related toxicity. The liver was identified as a possible target organ. Subchronic exposure to 2,4-DCP at drinking water concentrations of 0.2, 0.6, and 2.0 mg/ml (limit of solubility and acceptability was 2.0 mg/ml) for 90 days (approximate doses of 50, 150, 500 mg/kg/day) failed to induce significant compound related toxicity. The data presented and a review of the available literature support the relatively low order of toxicity of most chlorinated phenols ingested orally (except PCP).

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT Release to public	19. SECURITY CLASS (This Report) unclassified	21. NO. OF PAGES 22
	20. SECURITY CLASS (This page) unclassified	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

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INTRODUCTION

Chlorinated phenols (CPs) have been used as chemical intermediates in the manufacture of many products. Some have been used as antiseptics since 1893, whereas others are used as fungicides and preservatives in non-food items.

The U.S.E.P.A. and other regulatory bodies and organizations involved with the safety of drinking water are interested in these compounds because they are sometimes found in finished water and because there is a relative paucity of toxicological data concerning them. They do not appear to be a severe problem in drinking water for a number of reasons: (1) organoleptic properties - they affect the taste of the water and intake would be self-limiting; (2) the limited solubility of some of these compounds in water; (3) available toxicological data suggest that they generally are not highly toxic.

The CPs are formed from the breakdown of chlorobenzenes and from the chlorination of water containing phenol. The medicinal odor and taste of water is often due to CPs.

In conjuction with the U.S.E.P.A., selected literature was reviewed and a series of investigations were conducted to evaluate the acute and subchronic toxicity of a selected number of chlorinated phenols. The physical and chemical characteristics of a series of chlorinated phenols and those investigated in our program are listed in Table 1.

Experimental Design

The basic experimental design consisted of an evaluation of the effects of orally administered chlorinated phenols in mice and rats. These species were

selected because of their sensitivity to xenobiotics, size, cost and ease of handling. The agents tested were selected by the U.S.E.P.A. Exposures were either acute, repeated or subchronic and by either gavage or in drinking water. Details of the major procedures used are summarized in Tables 2, 3 and 4 and in Figure 1.

RESULTS

The acute oral toxicity data are summarized in Table 5. These data indicate that pentachlorophenol is the most toxic and the dichlorophenols the least toxic.

2-Chlorophenol was evaluated following 14 days of exposure at doses of 35, 69 and 175 mg/kg/day administered by stomach tube. The data are summarized in Table 6. 2,4-Dichlorophenol was evaluated following 14 and 90 days of exposure. The exposure levels for the repeated dosing 14-day study were 64, 128, and 638 mg/kg/day and for the subchronic study they were 50, 150, and 500 mg/kg/day. The test compounds were administered by gavage for the 14-day study and in the drinking water for the subchronic study. The data are summarized in Tables 7 and 8.

At the termination of the 2,4-DCP subchronic exposure study, 10 males and 10 females per group were randomly selected for an *in vivo* fertility study. Dosing was continued throughout mating and gestation. Eighteen days after mating, all females were sacrificed and the following parameters were measured or calculated:

Total implants
Total resorptions
Total number live pups
Weight of individual pups
Fertility index

The data are summarized on Table 9. The increased resorption rate at the mid dose is not statistically different from the vehicle control. There were no consistent adverse compound related effects.

In vitro reproductive data are summarized in Table 10.

The effects of exposure to selected chlorinated phenols on sister chromatid exchange (SCE) are summarized in Table 11.

DISCUSSION

Acute Toxicity. Available acute oral toxicity data of phenol and chlorinated phenols in mice and rats are summarized in Table 12. These compounds are not highly toxic, with the exception of pentachlorophenol. The order of toxicity (most to least) is: PCP > tetrachlorophenols > monochlorophenols > trichlorophenols > dichlorophenols. The order is similar in both mice and rats and suggests similar species sensitivity. The effects produced by these compounds, in both species and in both sexes, are also similar suggesting similar mechanisms of action. Increased respiration, motor weakness, tremors, CNS depression, convulsions, dyspnea, coma and then death were observed. Body temperature was decreased with the mono- and di-chlorophenols but was increased with the other chlorophenols.

Short Term Repeated Dosing. 2-CP at a dose of 175 mg/kg/day was lethal. At doses of 35 and 69 mg/kg/day, slight toxic effects were noted among the females only. The 2,4-DCP data essentially confirm and extend the findings of Kobayashi et al. (7) whose mice received 667 mg 2,4-DCP/kg b.w. for 10 days without evidence of any adverse effect. The liver appeared to be a target organ in both studies.

Subchronic Toxicity. The data presented confirm and extend the earlier work of Kobayashi et al. (7). They exposed mice for 6 months to doses of 45, 100 or 230 mg/kg/day. The only effect reported was non-specific microscopic liver changes. In the studies from our laboratories, the highest concentration that the animals would accept was 2.0 mg/ml using 10% Emulphor as the vehicle (resulting in a dose of 500 mg/kg/day). No significant biological effects were observed.

In Vitro Reproductive Effects. Eight chlorophenols were evaluated. Penetration was depressed by the 2,5-DCP, 3,4-DCP and 3,5-DCP at the highest concentration tested (1.0 mM). 2,4-DCP was inactive in vitro. Sperm and ova were removed from the animals exposed subchronically and evaluated. There were no effects on penetration. The in vivo findings confirm the in vitro effects.

Sister Chromatid Exchange. There were no adverse effects on SCE of mice exposed either acutely or for 14 or 90 days.

SUMMARY AND CONCLUSIONS

1. Chlorophenols (except pentachorophenol) demonstrate a relatively low order of toxicity.
2. The order of toxicity in mice and rats (most to least) is:

   PCP > tetra CPs > mono CPs > tri CPs > di CPs.
3. Short term (14 days) repeated exposure to 2-CP at (gavage) doses of 35, 69 or 175 mg/kg/day (approximately 1/10, 1/5, 1/2 the acute oral LD_{50}) resulted in 100% lethality at the highest dose and no biologically significant compound related effects at the lower doses.
4. Short term (14 days) repeated exposure to 2,4-DCP at (gavage) doses of 64, 128 or 638 mg/kg/day (approximately 1/20, 1/10, 1/2 the acute oral LD_{50}) failed to induce significant compound related toxicity. The liver was identified as a possible target organ.
5. Subchronic exposure to 2,4-DCP at drinking water concentrations of 0.2, 0.6 and 2.0 mg/ml (limit of solubility and acceptability was 2.0 mg/ml) for 90 days (approximate doses of 50, 150, 500 mg/kg/day) failed to induce significant compound related toxicity.
6. The data presented and a review of the available literature support the relatively low order of toxicity of most chlorinated phenols ingested orally (except PCP).

Table 1

PHYSICAL AND CHEMICAL PROPERTIES OF PHENOL AND CHLORINATED PHENOLS

	Formula	M.W.	Physical State	S.G.	M.P.°C	B.P.°C	Solubility Water (pph)	Alc.	Ether	pKa
Phenol	C_6H_5OH	94.11	Crystals	1.072	41	182	8.2 at 15° at 63.3°	S	VS	9.89
2-CP	ClC_6H_4OH	128.56	Liquid	1.241 (18/15°C)	α -7; β -0; γ -4.1	175-6	2.85	S	S-alk	8.65
3-CP	ClC_6H_4OH	128.56	Needles	1.268 (25°C)	32-33	214	2.6	S	S	8-12
4-CP	ClC_6H_4OH	128.56	Needles	1.306 (20/4°C)	41-43	217	2.7	VS	VS	9.37
2,3-DCP	$Cl_2C_6H_3OH$	163.01	Needles	1.383 (60/25°)	45	209-10	0.45	VS	VS	
2,4-DCP	$Cl_2C_6H_3OH$	163.01	Hexagonal Needles		45	206-208	SS	VS	VS	7.85
2,5-DCP	$Cl_2C_6H_3OH$	163.01	Prisms		59	211°	SS	VS	VS	7.50
2,6-DCP	$Cl_2C_6H_3OH$	163.01	Needles		68-69	219-220	...	VS	VS	6.91
3,4-DCP	$Cl_2C_6H_3OH$	163.01	Needles		68	253.5	...	...	...	8.58
3,5-DCP	$Cl_2C_6H_3OH$	163.01	Prisms		68	233°	SS	V	...	

Continued on next page

Table 1: PHYSICAL AND CHEMICAL PROPERTIES OF PHENOL AND CHLORINATED PHENOLS (Continued)

	Formula	M.W.	Physical State	S.G.	M.P.°C	B.P.°C	Solubility Water (pph)	Alc.	Ether	pKa
2,3,5-TCP	$Cl_3C_6H_2OH$	197.46	Needles		55	249-50	Sl.S.	S	S	
2,4,5-TCP	$Cl_3C_6H_2OH$	197.46	Needles		61-63	252	I	S	S	7.07
2,3,6-TCP	$Cl_3C_6H_2OH$	197.46	Needles		58°	...	S	V	V	5.98
2,4,6-TCP	$Cl_3C_6H_2OH$	197.46	Needles		68-69	246	0.09	VS	VS	6.62
3,4,5-TCP	$Cl_3C_6H_2OH$	197.46	Needles		101	271-277	...	S	...	7.83
2,3,4,5-TCP	Cl_4C_6HOH	231.90	Needles	1.6 (60/4°C)	69-70	164	Sl.S	VS	VS	
2,3,4,6-TCP	Cl_4C_6HOH	231.90	Needles		70	150				5.46
2,3,5,6-TCP	Cl_4C_6HOH	231.90	Leaflets		115°	...				
2,3,4,5,6-PCP	Cl_5C_6OH	266.35	Solid	1.85 (22°C)	188-89	310				5.00

Table 2

EXPERIMENTAL DESIGN

Acute Oral Toxicity Study

Animals:

Adult male and female CD-1 ICR mice; healthy, acclimated, randomized
Adult male and female CD rats; healthy, acclimated, randomized
Overnight (18 hours) fast (water, no food)
10 males, 10 females per dosage level; 5 levels

Housing: 1/plastic shoebox cage with hardwood sawdust bedding
Feed: Purina Rodent Chow No. 5001; deionized water (in bottles)
Environmental Conditions:
Rooms: 22° ± 2°C; relative humidity: 40-60%
Light Cycle: 12 light/12 dark (7:00 a.m. - 7:00 p.m.)

Test Material:

Identity confirmed
Prepared day of administration
Administered by gavage (stomach tube)
Volume: 10 ml/kg body weight

Specific Conditions:

Food withheld for 2 hours after dosing
Continuous observations for 1 hour after dosing, hourly for next 4 hours and twice daily for the next 14 days
Cageside observations include changes in behavior, respiration, circulation, skin and fur, eyes, mucous membranes; evidence of tremors or convulsions, lethargy, sleep, coma, salivation, diarrhea; time of onset of changes and duration; time of death
All animals that died during the observation period and the survivors were necropsied

Calculations of LD_{50}:

Log Probit Analysis of Finney (1)
Litchfield-Wilcoxon (2)

Table 3

EXPERIMENTAL DESIGN

Short Term (14-days) Repeated Oral Dosing Study

Animals:

Adult male and female CD-1 ICR mice; healthy, acclimated, randomized; earpunched for identification
Adult male and female CD rats; healthy, acclimated, randomized
10 males, 10 females per dosage level; 5 levels

Housing: 1/plastic shoebox cage with hardwood sawdust bedding
Feed: Purina Rodent Chow No. 5001; deionized water (in bottles)
Environmental Conditions:
Rooms: 22° ± 2°C; relative humidity: 40-60%
Light Cycle: 12 light/12 dark (7:00 a.m. - 7:00 p.m.)

Test Material:

Identity confirmed
Prepared day of administration (gavage) or twice weekly (drinking water)
Vehicles: water, corn oil, Emulphor
Gavage: 10 ml/kg/body weight; Drinking Water: chemical, toxicological or palatability limit

Specific Conditions:

Groups: Controls: naive, vehicle, positive (occasionally);
3 treated groups, at least 20 males and 20 females per group
Cageside observations: twice daily; behavior, morbidity; mortality; exceptions noted
Body weights: onset, days 8 and 15 and at necropsy
Fluid consumption: twice weekly (unless gavaged)
Hematology: blood collected at necropsy; wbc (total, differential); rbc, platelets, HCrt, Hb, coagulation
Serum chemistries: LDH, SGPT, SGOT, SAP, BUN, bilirubin, protein, glucose, cholesterol, ALB/GLOB, P, Ca, Na, Cl, K
Liver microsomal activities: cytochrome P_{450}, cytochrome B_5, microsomal protein, aminopyrine demethylase, aniline hydroxylase, arylhydrocarbon hydroxylase
Immune response
Genetic toxicology: testicular DNA synthesis and sperm morphology; SCE (testes, bone marrow); mitotic index (bone marrow)
Reproductive toxicology: *in vitro* penetration, fertilization, blastula formation
Activity and behavioral measurements
Necropsy: gross observations; organ weights
Statistical Analysis: appropriate tests including Bartlett's Test for Homogeneity, Parametric ANOVA, Dunnett's Multirange Test, Wilcoxon Non-Parametric Test; Significance: $p \leq 0.05$

Table 4

EXPERIMENTAL DESIGN

Subchronic Oral Toxicity Study (90-Days)

Animals:

Adult male and female CD-1 ICR mice; healthy, acclimated, randomized; earpunched for identification
10 males, 10 females per dosage level; 5 levels

Housing: 1/plastic shoebox cage with hardwood sawdust bedding
Feed: Purina Rodent Chow No. 5001; deionized water (in bottles)
Environmental Conditions:
Rooms: $22^{o} \pm 2^{o}C$; relative humidity: 40-60%
Light Cycle: 12 light/12 dark (7:00 a.m. - 7:00 p.m.)

Test Material:

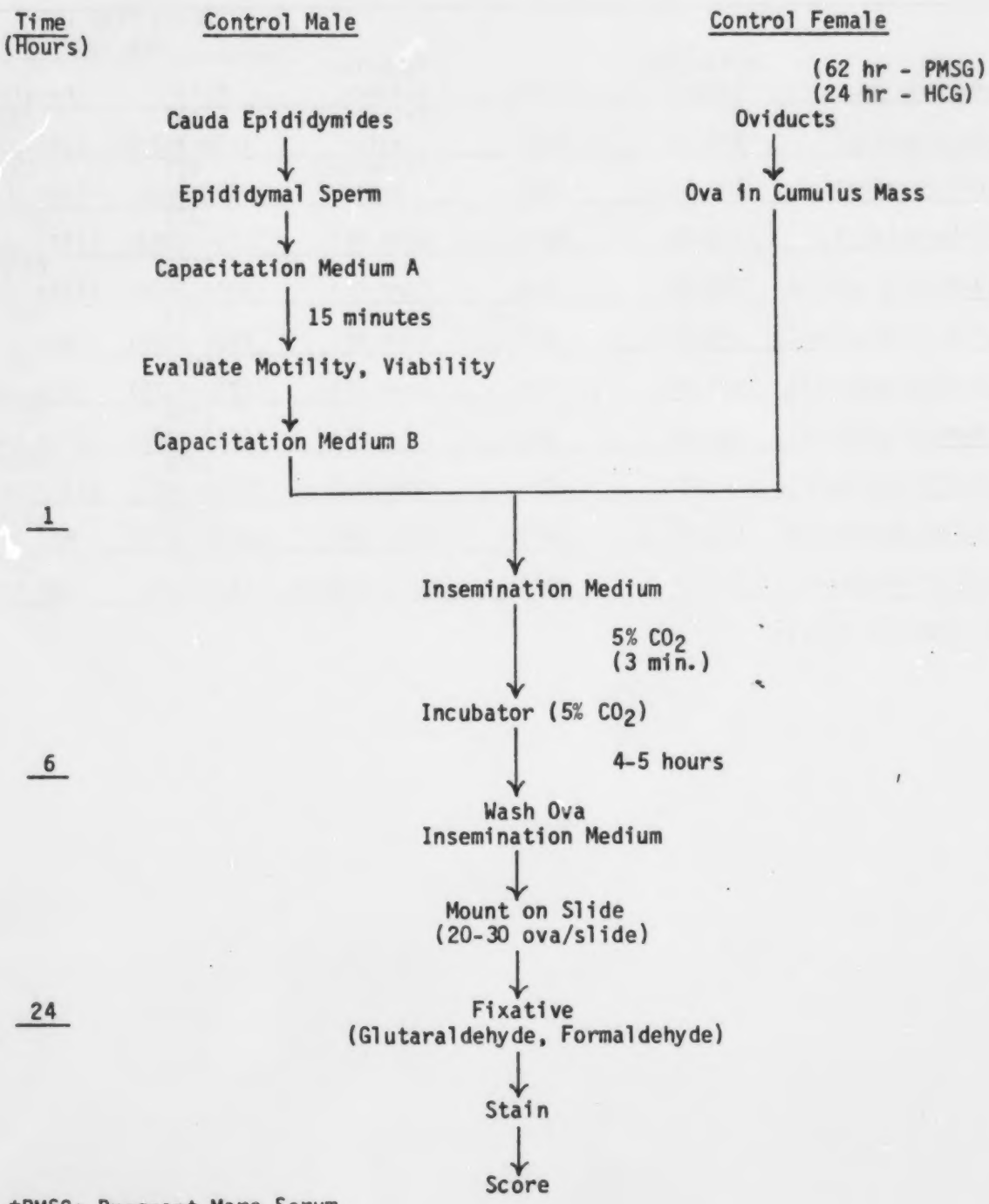
2,4-dichlorophenol
Identity confirmed
Prepared twice weekly (drinking water)
Vehicle: Emulphor (10%, aqueous)

Specific Conditions:

Groups: Controls: naive, vehicle, positive (cyclophosphamide); 3 treated groups, at least 20 males and 20 females per group
Cageside observations: twice daily; behavior, morbidity, mortality, exceptions noted
Body weights: onset, once weekly and at necropsy
Fluid consumption: twice weekly
Hematology: blood collected at necropsy; wbc (total, differential); rbc, platelets, HCrt, Hb, coagulation
Serum chemistries: LDH, SGPT, SGOT, SAP, BUN, bilirubin, protein, glucose, cholesterol, ALB/GLOB, P, Ca, Na, Cl, K
Liver microsomal activities: cytochrome P_{450}, cytochrome B_5, microsomal protein, aminopyrine demethylase, aniline hydroxylase, arylhydrocarbon hydroxylase, ethoxycoumarin-O-deethylase, testosterone hydroxylation, cytochrome c reductase
Genetic toxicology: testicular DNA synthesis and sperm morphology; SCE (testes, bone marrow); mitotic index (bone marrow)
Reproductive toxicology: *in vitro* penetration, fertilization, blastula formation
Activity and behavioral measurements
Necropsy: gross observations; organ weights
Statistical Analysis: appropriate tests including Bartlett's Test for Homogeneity, Parametric ANOVA, Dunnett's Multirange Test, Wilcoxon Non-Parametric Test; Significance: $p \leq 0.05$

Figure 1

IN VITRO PENETRATION AND FERTILIZATION SCHEME



*PMSG: Pregnant Mare Serum Gonadotrophin
HCG: Human Chorionic Gonadotrophin

Table 5

ACUTE ORAL TOXICITY OF CHLOROPHENOLS
IN CD-1 MICE

Compound	Molecular Weight	Purity	Vehicle/ Solvent	Acute Oral LD_{50} (mg/kg) Male	Female
2-Chlorophenol	128.56	98+%	Deionized Water	347 (239-393)[a/]	345 (321-381)[a/]
3-Chlorophenol	128.56	99%	Deionized Water	521 (463-586)	530 (468-601)
4-Chlorophenol	128.56	99+%	Corn Oil	1373 (1191-1583)	1422 (1333-1518)
2,3-Dichlorophenol	163.00	98%	Corn Oil	2585 (2046-3266)	2376 (2186-2585)
2,4-Dichlorophenol	163.00	99%	Corn Oil	1276 (982-1569)	1352 (1094-1670)
2,5-Dichlorophenol	163.00	98%	Corn Oil	1600 (1233-2075)	946 (623-1438)
2,6-Dichlorophenol	163.00	99%	Corn Oil	2198 (1727-2797)	2120 (1799-2498)
3,4-Dichlorophenol	163.00	99%	Corn Oil	1685 (1504-1887)	2046 (1472-2846)
3,5-Dichlorophenol	163.00	99%	Corn Oil	2643 (2269-3078)	2389 (1829-3120)
Pentachlorophenol	226.34	99+%	10 Emulphor	177 (125-252)	117 (65-212)

[a/] Confidence limits

Table 6

SHORT-TERM REPEATED DOSING (14 DAYS)
2-CP, MICE

Animals: 12 males, 12 females per group

Exposure Levels: Naive control; vehicle control (corn oil); 35, 69, 175 mg/kg/day; positive control (cyclophosphamide, 25 mg/kg)

Body Weights: Days 1, 8, 15; lower at 69 mg/kg

Mortality: All died at 175 mg/kg

Organ Weights and Ratios: Females only - ↓ brain, liver, spleen

Hematology: NCRE*

Clinical Chemistry: NCRE

Hepatic Microsomal MFO Activity: NCRE

Immune Response, cell mediated and humoral: NCRE

Behavioral Parameters: Hyperactivity at both doses

Sister Chromatid Exchange: NCRE

Gross Pathological Findings: None

*NCRE - No biologically or statistically significant compound related adverse effects

Table 7

SHORT-TERM REPEATED DOSING (14 DAYS)
2,4-DCP, MICE

Animals: 12 males, 12 females per group

Exposure Levels: Naive control; vehicle control (corn oil); 64, 128, 638 mg/kg/day; positive control (cyclophosphamide, 25 mg/kg)

Body Weights: Days 1, 8, 15 - NCRE*

Mortality: 1 male at the 638 mg/kg level - NCRE

Organ Weights and Ratios: NCRE

Hematology: NCRE (↑ in platelets at 638 mg/kg)

Clinical Chemistry: ↑ bilirubin among all treated females only; slight ↑ in SGOT, SGPT in male mice at mid dose

Hepatic Microsomal MFO Activity: ↑ glutathione, ↑ microsomal protein, ↑ cytochrome b_5 among females and males at 638 mg/kg dose

Behavioral Parameters: NCRE

Sister Chromatid Exchange: NCRE

Gross Pathological Findings: None

*NCRE - No biologically or statistically significant compound related adverse effects.

Table 8

SUB-CHRONIC ORAL TOXICITY (90 DAYS)
2,4-DCP, MICE

Animals: 20 males, 20 females per group

Exposure Levels: Naive control (deionized water); vehicle control (10% emulphor); 0.2, 0.6, 2.0 mg/ml drinking solution (equivalent to 50, 150, 500 mg/kg b.w./day)

Fluid Consumption: Measured twice weekly - naive controls (M and F) had highest fluid intake; treated females consumed more than vehicle controls

Body Weights: Weekly - NCRE*

Mortality: 1 at 150 mg/kg - NCRE

Organ Weights and Ratios: NCRE

Hematology: NCRE

Clinical Chemistry: NCRE

Hepatic Microsomal MFO Activity: NCRE

Sister Chromatid Exchange: NCRE

Behavioral Parameters: NCRE

Gross Pathological Findings: None

In vitro Penetration: NCRE

Reproductive Effects: NCRE

*NCRE - No biologically or statistically significant compound related adverse effects.

Table 9

REPRODUCTIVE EFFECTS OF 90-DAY TREATMENT
WITH 2,4-DICHLOROPHENOL

	F.I.*	Total No. Implants	Total No. Resorptions	Total No. Live Pups	Mean Litter Size	Mean Pup Wt. (grams)
Control (naive)	90	198	5	193	11	1.08
10% Emulphor	75	166	12	154	10	1.09
0.2 mg/ml	80	181	1	180	11	1.01
0.6 mg/ml	90	198	16	182	10	1.13
2.0 mg/ml	65	160	1	159	12	1.11

*Fertility Index = $\frac{\text{Number of Pregnant Females}}{\text{Number of Females Mated}} \times 100$

Table 10

PERCENT PENETRATION (MEAN ± S.E.M.) OF MOUSE OVA FOLLOWING EXPOSURE TO VARIOUS CHLOROPHENOLS AT THREE CONCENTRATIONS

	COMPOUND								
Treatment	2-CP	3-CP[d]	2,3-DCP	2,4-DCP	2,5-DCP	2,6-DCP	3,4-DCP	3,5-DCP	$CdCl_2$
Control	65 ± 6 (90)	58 (41)	68 ± 5 (158)*	76 ± 5 (128)	75 ± 3 (135)	78 ± 4 (190)	78 ± 4 (218)	62 ± 0 (181)	66 ± 6 (393)
0.1 mM	65 ± 1 (57)	82 (40)	74 ± 1 (131)	74 ± 10 (100)	82 ± 5 (90)	83 ± 5 (132)	71 ± 14 (140)	66 ± 2 (115)	58 ± 7 (427)
0.3 mM	65 ± 5 (94)	50 (28)	82 ± 6 (95)	57 ± 6 (112)	79 ± 5 (155)	78 ± 3 (145)	64 ± 9 (163)	53 ± 3 (121)	26 ± 7[b] (219)
1.0 mM	65 ± 1 (91)	68 (28)	78 ± 3 (104)	60 ± 8 (124)	58 ± 3[b] (131)	67 ± 5 (150)	8 ± 7[b] (138)	7 ± 3[b] (109)	4 ± 2[b,c] (156)
F-Value	1.41		1.36	1.22	5.00[a]	1.85	8.24[a]	18.68[a]	11.01[a]

*Total ova observed in 4-5 experiments.

[a]This F-value is significant at $P \leq 0.05$.

[b]Significantly different from control.

[c]Concentration of $CdCl_2$ is 0.6 mM in this experiment.

[d]One experiment.

Table 11

SISTER CHROMATID EXCHANGE RESPONSE
FOLLOWING EXPOSURE TO CHLORINATED PHENOLS*

Compound	Route of Administration	Duration	Response
2,3-DCP	I.P.	24 hrs	-- **
2,4-DCP	I.P.	24 hrs	-- **
2,4-DCP	Drinking Water	24 hrs	-- **
2,5-DCP	I.P.	24 hrs	± ***
2,6-DCP	I.P.	24 hrs	-- **
3,4-DCP	I.P.	24 hrs	-- **
PCP	I.P.	24 hrs	-- **

*I.P. injections are routinely employed as a standard pre-drinking water exposure screen. This may become important when pharmacokinetic considerations are brought to bear on the problem. To date, a descrepency between the data obtained by either route of exposure has not been found.

**The compound was negative in the SCE assay.

***In order to be considered a positive compound in the SCE assay, the results must exhibit a dose response relationship and be two times greater than background. With 2,5-DCP a dose response was established but we were unable to achieve a two-fold increase in the SCE level due to toxicity.

Table 12

ACUTE ORAL TOXICITY (LD_{50}) OF PHENOL AND CHLORINATED PHENOLS

	Mouse (mg/kg)		Rat (mg/kg)	
	Male	Female	Male	Female
Phenol	300 (3)*	---	530 (4)	---
2-CP	347 (5), 670 (6)	345 (5)	670 (7)	---
3-CP	521 (5)	530 (5)	570 (7)	---
4-CP	1373 (5)	1422 (5)	670 (7), 261 (8)	---
2,3-DCP	2585 (5)	2376 (5)	---	---
2,4-DCP	1276 (5), 1630 (10)	1352 (5)	580 (7), 2830 (10), 4000 (9)	---
2,5-DCP	1600 (5)	946 (5)	---	---
2,6-DCP	2198 (5)	2120 (5)	2940 (8)	---
3,4-DCP	1685 (5)	2046 (5)	---	---
3,5-DCP	2643 (5)	2389 (5)	---	---
2,3,5-TCP	---	---	---	---
2,4,5-TCP	---	---	820 (7), 1620 (8)	---
2,3,6-TCP	---	---	---	---
2,4,6-TCP	---	---	820 (8)	---
3,4,5-TCP	---	---	---	---
2,3,4,5-TCP	400 (8)	---	140 (7)	---
2,3,4,6-TCP	---	---	---	---
2,3,5,6-TCP	109 (8)	---	---	---
PCP	177 (5)	117 (5)	80 (7), 78 (10), 146 (11)	175 (11)

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